THE ROLE OF ADRENAL STEROIDS ON RENAL FUNCTION AND ELECTROLYTE METABOLISM*

The Fourth Harlow Brooks Lecture

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THE adrenal cortex is intimately concerned with electrolyte and water metabolism and, either directly or indirectly, with certain aspects of renal function. With the isolation and identification of various adrenal cortical fractions, it became possible to subject this aspect of adrenal function to more precise study. The results of these studies over the past quarter of a century have yielded a voluminous and, by and large, contradictory and confusing literature. Certain generalities have of course become evident. Even prior to the availability of specific adrenal steroidal fractions it had been adequately established that the lack of adrenal function in the patient with Addison's disease and in the adrenalectomized animal resulted in an increased urinary excretion of sodium and chloride with equivalent amounts of water, and a decrease in the urinary excretion of potassium. When this basic defect was later subjected to more careful scrutiny with improved techniques, it became evident that the defect in relation to electrolyte and water metabolism consisted of at least three component abnormalities: 1) a decrease in the glomerular filtration rate and renal plasma flow;[1,2] 2) an inability adequately to handle a water load over a given period of time; and 3) an increase in the urinary loss

*Presented by Dr. Soffer at the 29th Graduate Fortnight of The New York Academy of Medicine, October 23, 1956. On this occasion, Dr. Soffer received the Harlow Brooks Medal.

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Aided by a grant from the National Institutes of Health of the U. S. Public Health Service. Research grant number A-921 (R).

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of sodium and chloride and a decrease in the urinary excretion of potassium. The question promptly arose as to whether the inability of the untreated patient with Addison's disease or the adrenalectomized animal to handle a water load represented a renal tubular defect, a reduction in the glomerular filtration rate, a change in the renal plasma flow, or various combinations of these several factors. Similarly, attempts were made to relate the abnormalities in electrolyte metabolism to changes in renal function. When the various adrenal hormones became available, studies were instituted to investigate their individual effects on these specific functions.

The contradictory results of these studies on electrolyte metabolism and renal function are due to a variety of factors, including: 1) the presence or absence of the adrenals; 2) the dosage and duration of treatment; 3) the daily salt intake; 4) the mode of administration; and 5) species differences.

Effects of Adrenal Steroids on Electrolyte Metabolism and Renal Function in Adrenal Insufficiency

In the patient with Addison's disease and in the adrenalectomized animal the administration of desoxycorticosterone is followed by a decrease in the urinary excretion of sodium, an increase in the urinary excretion of potassium, an elevation in the serum sodium level, and a reduction in the serum potassium content. However, despite the ability of this steroid to correct the electrolyte imbalance with respect to sodium and potassium, it fails to exercise an effect on the inability of the adrenalectomized animal or patient with Addison's disease to adequately handle a water load within a given period of time. In addition, the reduction in the glomerular filtration rate and the renal plasma flow cannot be completely corrected by the administration of desoxycorticosterone alone, both during short term studies[3-5] and more prolonged periods of administration.[3] This situation is altered, however, when the degree of hydration is increased appreciably.[3] The reduction in the glomerular filtration rate following upon adrenalectomy can be corrected by adequate maintenance with saline[6] (Table I). Similarly, the administration of excessive amounts of desoxycorticosterone in association with an adequate salt intake may result in an increase in the glomerular filtration rate approximating normal levels providing significant sodium and water retention occurs.[3]

TABLE I—GLOMERULAR FILTRATION RATES OF FIVE DOGS IMMEDIATELY BEFORE AND 8 TO 10 DAYS AFTER ADRENALECTOMY, ADEQUATELY MAINTAINED WITH SALINE

	Glomerular Filtration Rate (ml./min.)	
Dog. No.	*Control*	*After Adrenalectomy*
1	61.8	61.9
2	34.6	31.2
3	53.9	48.7
4	63.3	59.7
5	57.6	61.0

Adapted from Roemmelt, J. C., Sartorius, O. W., and Pitts, R. F.: Excretion and Reabsorption of Sodium and Water in the Adrenalectomized Dog. Amer. J. Physiol., 159:124, 1949. (Ref. 6.)

This is in considerable contrast to the results observed with cortisone. The administration of this agent to adrenalectomized animals results, within a matter of hours, in a significant increase in both the renal plasma flow and glomerular filtration rate. The increase in the glomerular filtration rate thus observed may occur in the absence of any increase in the plasma volume and in the face of a negative sodium balance.[3, 5]

The fact that in adrenal insufficiency the glomerular filtration rate may be enhanced by the adequate administration of saline would suggest that the reduction in glomerular filtration is at least in part related to the loss of sodium and extracellular fluid. Although this is indeed an important factor, the fact remains that cortisone is capable of improving the defect in glomerular filtration over a period of time during which no significant changes in the extracellular compartment or plasma volume could be expected to take place. It is in this sense that its effect on this particular renal function is different from that exerted by desoxycorticosterone. The role of this latter hormone on the glomerular filtration rate is essentially an indirect one, related to its ability to cause a retention of electrolyte and water.

This specificity of effect of cortisone is similarly demonstrated in its influence on the renal response to water loading in adrenal insufficiency. No amount of desoxycorticosterone will increase the five-hour urine volume following the imbibing of a water load. However, under similar

TABLE II—EFFECT OF CORTISONE ON WATER LOADING RESPONSE AND GLOMERULAR FILTRATION RATE IN ADRENAL INSUFFICIENCY

	1500 ml. of water		*1500 ml. of water +50 mg. cortisone*	
Subject	*5 hour urine volume ml.*	*Creatinine clearance (cc./min.)*	*5 hour urine volume (ml.)*	*Creatinine clearance (cc./min.)*
U.D. (A)	390	99	760	97
G.M. (H)	420	89	1025	103
C.S. (H)	217	56	1000	63
S.G. (H)	640	85	980	89

(A) = Addison's disease
(H) = Hypopituitarism with adrenal insufficiency

test circumstances the prior administration of cortisone will invariably result in a significant increase in the urine volume approximating that obtained in normal individuals.[7] This effect of cortisone on the renal response to water loading can apparently occur independently of its effect on the glomerular filtration rate. In Table II are presented the data obtained in one patient with Addison's disease and three patients with hypopituitarism with adrenal insufficiency. In all four patients an appreciable increase in the urine volume occurred following the oral administration of 50 mg. of cortisone two hours before the test. In only one instance, however, was there a concomitant significant increase in the creatinine clearance. This, of course, does not exclude the probable effect of the rate of glomerular filtration on the maximal urinary flow in intact animals.[8] But in adrenal insufficiency there still is an additional factor, that of the influence of some adrenal hormones on the resorptive capacity of the distal tubular segment for water.

The available data would suggest that in adrenal insufficiency, desoxycorticosterone acetate exercises a considerable and fairly consistent effect on electrolyte and water exchange, in part by increasing the tubular reabsorption of sodium. The effects of cortisone on electrolyte metabolism are less consistent but this steroid specifically affects glomerular filtration and alters the resorptive capacity of the distal segment of the tubules for water.

The reduction in the glomerular filtration rate and renal plasma flow in adrenal insufficiency probably represents a homeostatic device to minimize salt and water loss, since one of the major renal defects in adrenal insufficiency is a decrease in the renal tubular absorption of sodium. Following the administration of various adrenal cortical fractions, the urinary loss of electrolyte becomes appreciably reduced, often, however, without any immediate change in the rate of glomerular filtration or renal plasma flow.[9] Conversely, other adrenal hormones may cause an increase in the glomerular filtration rate accompanied by increasing losses of urinary sodium[3,5] despite the fact that the expected enhancement of tubular absorption of sodium from 98 to over 99 per cent has occurred. This paradox may be resolved if we assume that the urine volume and its sodium content under the influence of adrenal steroid therapy are the mathematical resultant of: 1) the degree of change in the glomerular filtration rate; 2) the degree of change in the renal plasma flow; and 3) the degree of change in the absorptive capacity of the tubule for electrolyte and water.

One may further speculate on possible additional factors involved in the renal tubular resorptive capacity for water. In adrenal insufficiency this function is defective and capable of correction by cortisone but not by desoxycorticosterone. That this defect is probably not entirely related to a decrease in glomerular filtration is evidenced by the fact that an appreciable increase in the glomerular filtration rate by the administration of saline and desoxycorticosterone does not result in any improved response to water loading. On the other hand, there is considerable evidence to suggest that there is an actual increase in the tubular reabsorption of water in adrenal insufficiency.[6,10-13] Corey, Silvette, and Britton[14] have postulated that the adrenal cortical and the posterior pituitary hormones exercise antithetical effects. In effect, the adrenal fractions increase water and decrease sodium excretion, while the posterior pituitary antidiuretic hormone causes the reverse phenomenon. Roemmelt, Sartorius and Pitts[6] suggest that the increased urinary excretion of sodium occurring in adrenal insufficiency is a reflection of the effect of the antidiuretic hormone of the posterior pituitary made possible by the absence of adrenal hormones. Finally, several groups of investigators[15-18] have found evidence of increased amounts of an antidiuretic substance in adrenalectomized animals.

Regardless of whether there actually occurs an increase in circulating

TABLE III—THE EFFECT OF ETHYL ALCOHOL ON THE EXCRETION OF A WATER LOAD IN PATIENTS WITH ADRENAL INSUFFICIENCY

	1500 ml. of water	*1500 ml. of water +60 gm. alcohol*	*1500 ml. of water +50 mg. cortisone*
Subject	*5 hour urine volume ml.*	*5 hour urine volume ml.*	*5 hour urine volume ml.*
L.C. (A)	350	135	1190
U.D. (A)	390	435	760
G.M. (H)	420	375	1025

(A) = Addison's disease
(H) = Hypopituitarism with adrenal insufficiency

antidiuretic hormone, the hypothesis that enhanced tubular reabsorption of water is due to the action of an antidiuretic principle in the absence of adrenal hormones is an attractive one. The question arises as to the origin of this principle, and the first point of consideration, of course, is its possible identity with the antidiuretic hormone of the posterior pituitary. In Table III are presented the data obtained in three patients with adrenal insufficiency on whom water load tests were performed following the oral administration of ethyl alcohol. In none of the three did there occur a significant increase in the urine volume following the ingestion of alcohol, such as one might have expected if the active antidiuretic principle were of posterior pituitary origin. These studies included the administration of the total dose of 60 gm. of alcohol just prior to the administration of the water load, and were subsequently repeated distributing the alcohol equally through a 24 hour period before giving the water. Similar results have previously been reported in one patient with Addison's disease and one with hypopituitarism.[19]

One would hardly accept these data as unequivocal evidence negating the hypothesis. However, since ethyl alcohol has been shown to inhibit the release of antidiuretic hormone from the posterior pituitary gland[20-23] these results do raise two salient questions: 1) Is the circulating antidiuretic principle present in adrenal insufficiency of posterior pituitary origin? and 2) If this factor is of pituitary origin does it play the role in adrenal insufficiency outlined for it by the hypothesis? The

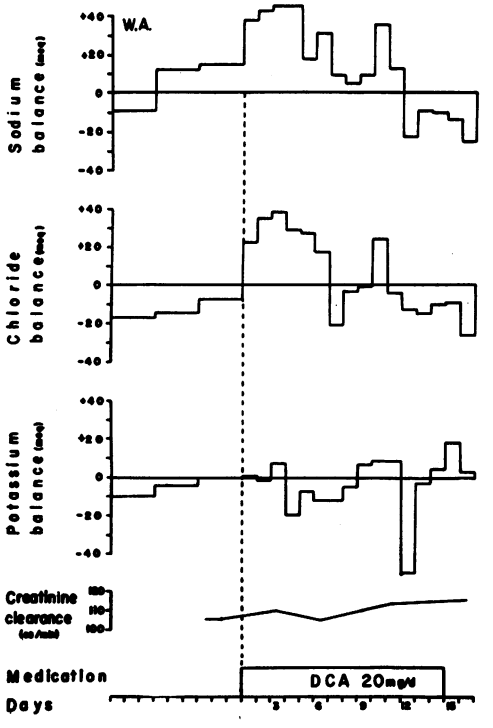

Figure 1—The effect of desoxycorticosterone acetate on sodium, chloride and potassium balance and creatinine clearance in a normal subject.

failure of ethyl alcohol to induce water diuresis following a water load would cast great doubt on the functional significance of the circulating antidiuretic principle in adrenal insufficiency if we assume it to be of posterior pituitary origin.

Effects of Adrenal Steroids on Electrolyte Metabolism and Renal Function in the Presence of Intact and Hyperfunctioning Adrenals

Some years ago we reported on the increased urinary excretion of sodium in some patients with Cushing's syndrome following administration of desoxycorticosterone acetate.[24, 25] This paradoxical observation raised the question of a possible different role of desoxycorticosterone in relation to electrolyte and water metabolism in the presence of intact

adrenals, in contrast to that observed in adrenal insufficiency. Several reports subsequently appeared describing the initial retention of sodium in adrenal intact individuals upon the administration of this hormone, followed by an increased urinary excretion of this electrolyte after 6 to 10 days of continued therapy with the steroid.[26, 27] In one of the reported studies, the salt intake was unrestricted, and in the other, the daily salt intake varied from 3.0 to 3.5 gm. In Figure 1 are presented the balance data that we obtained in a normal subject treated for 14 days with 20 mg. of desoxycorticosterone daily. The subject was maintained on an 8.5 milliequivalent sodium diet with a daily oral supplement of 3 gm. of salt. The period of treatment with desoxycorticosterone was preceded by an eight day control period on the fixed diet with the added daily salt supplement. During the first six days of therapy there occurred a considerable retention of sodium and chloride and some increase in the urinary excretion of potassium. During this six day period the glomerular filtration rate as measured by creatinine clearance remained constant and unchanged from the control period. From the 6th to the 11th day the degree of sodium retention became less. This was more marked with chloride, and a positive potassium balance was observed. From the 11th to the 14th day there was a definite negative sodium and chloride balance and a variable urinary excretion of potassium. From the 6th to the 14th day, concomitant with the increase in the urinary excretion of sodium and chloride, there was a very slight but consistent and progressive increase in the glomerular filtration rate, which reached a peak at the time of the maximum urinary loss of sodium and chloride. Such a progressive decrease in sodium retention with an eventual negative sodium balance within a 6 to 12 day period is not necessarily consistently observed in the presence of intact adrenals. In patients with adrenal cortical hyperfunction producing Cushing's syndrome an increase in the urinary excretion of sodium often, although by no means always, occurs almost immediately upon the administration of desoxycorticosterone.[24, 25] The significance of these observations is to emphasize the difference in effect, at least in time relationships, of the hormone desoxycorticosterone in the presence or absence of intact adrenals. The salt retaining effect of the steroid is in part modified by the presence of actively functioning adrenals.

Unlike desoxycorticosterone, the effect of cortisone on electrolyte metabolism in adrenal insufficiency is variable. In this respect, the be-

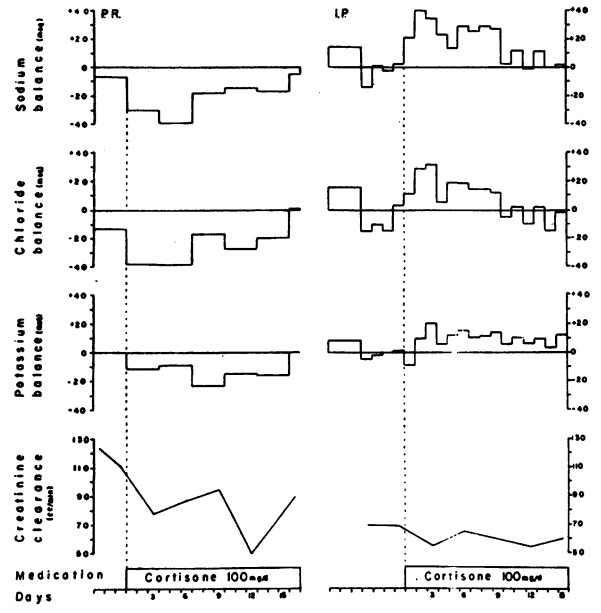

Figure 2—The effect of cortisone on sodium, potassium and chloride balance and creatinine clearance in two normal subjects.

havior of cortisone in the presence of intact adrenals is not very different from that observed in adrenal insufficiency. As with desoxycorticosterone, however, in the presence of intact adrenals the prolonged use of cortisone may result in an increase in the urinary excretion of sodium and chloride, although during the early period of treatment there may have been salt retention.[28, 29] In Figure 2 are presented the balance data that we obtained in two normal subjects treated with the oral administration of 100 mg. of cortisone divided into four equal daily doses, for a 15 day period in one instance and a 17 day period in the other. They were maintained on a constant diet containing 8.5 milliequivalents of sodium with a daily added salt supplement of 3 grams. In the patient P.R. there was an immediate negative sodium, chloride, and potassium balance. The sodium and chloride loss was greatest during the first six days of therapy and then became progressively less, approximating the initial control levels toward the end of the period of study. Throughout the study the glomerular filtration rate, although variable, tended to be lower than during the control period. In the second patient (I.P.) there

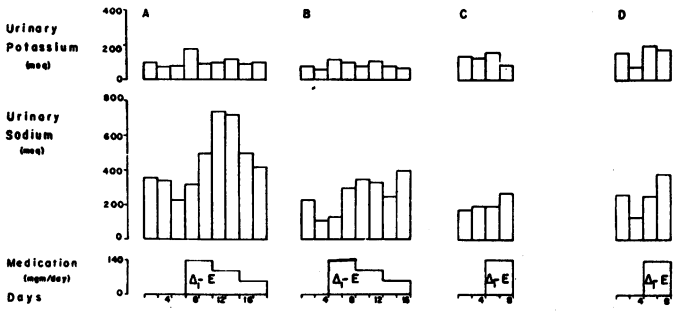

Figure 3—Effect of prednisone on the urinary excretion of sodium and potassium.

was an initial sodium, chloride, and potassium retention, most marked during the first eight days of treatment, followed by a lesser degree of retention of sodium and potassium through the remainder of the study, with a slightly negative chloride balance. The glomerular filtration rate did not alter significantly during the experimental period.

The introduction of an unsaturated double bond between carbons 1 and 2 in ring "A" of cortisone and cortisol alters the effect of the steroid on electrolyte metabolism. In Figure 3 are presented such data in four normal subjects maintained on a constant daily sodium intake of 8.5 milliequivalents with an added supplement of 3.0 gm. of salt. Following a control period of six days on this regimen, they were then given 40 to 140 mg. of prednisone daily by mouth for a 4 to 12 day period. In all four subjects there followed, to varying degrees, an increase in the urinary excretion of sodium and a very slight over-all increase in the urinary excretion of potassium. This study was subsequently repeated in four additional normal subjects, using prednisolone in a daily dosage of 140 mg. for four days (Fig. 4). In three members of this group, there again occurred a definite increase in the urinary excretion of sodium. In the fourth subject, no significant change occurred. In all four subjects the urinary excretion of potassium was slightly increased.

The nature of the changes in the extracellular compartment following administration of cortisone to subjects with intact adrenals is of considerable interest. In such individuals on a comparatively salt-free

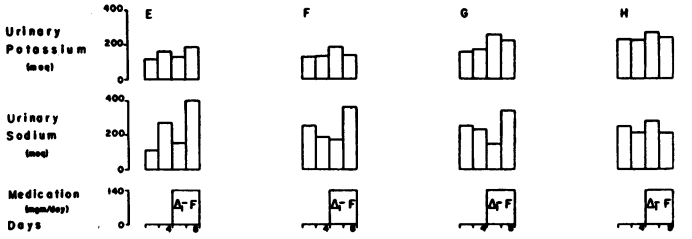

Figure 4—Effect of prednisolone on the urinary excretion of sodium and potassium.

diet (3 to 8.5 milliequivalents of sodium daily) the extracellular compartment was increased following the administration of cortisone. This increase was not associated with a gain in weight, and, therefore, represented a shift of fluid from within the cells outward.[30, 31] Further extension of this study[31] during which subjects with intact adrenals received 100 to 200 mg. of cortisone daily for 10 to 20 days revealed a progressive increase in the inulin space, which reached a peak increase of approximately 23 per cent after eight to nine days and spontaneously reverted to control values by the 12th to 15th day despite continued therapy. The expansion of the inulin space was associated with an increase in total extracellular sodium and chloride but no gain in weight. When the extracellular volume began to fall during the period of treatment there was a proportionate decrease in extracellular electrolytes, not accompanied by a corresponding negative sodium and chloride balance. These data again suggest a transient shift of fluid, sodium, and chloride from within the cell to the extracellular space under the influence of cortisone. Thorn and his co-workers[32] suggest that this effect of cortisone tends to restore towards normal the elevated intracellular sodium characteristic of many chronic disease states. The shift of sodium from within the cell to the extracellular compartment serves to increase the load of sodium presented to the kidney for excretion. Some of the sodium thus presented in the tubule is excreted and the remainder again re-absorbed.

Similar changes in shifts of electrolytes and fluid in the presence of intact adrenals were also obtained with desoxycorticosterone.[33] In one patient with Cushing's syndrome due to adrenal cortical hyperfunction without tumor, however, the oral administration of cortisone was fol-

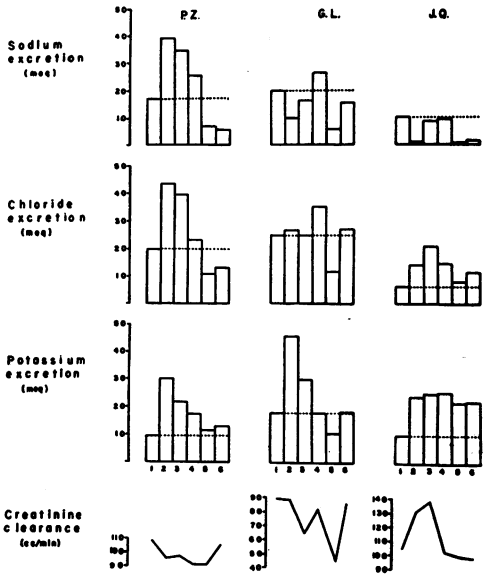

Figure 5—Acute effects of adrenal steroids on urinary excretion of sodium, potassium and chloride: 1) control; 2) cortisone; 3) prednisone; 4) compound "S"; 5) aldosterone; 6) desoxycorticosterone acetate.

lowed by a decrease in the extracellular compartment as measured by thiosulfate; this became evident within three days after the beginning of the experiment and was not associated with a previous increase in the extracellular fluid. In this experiment there occurred no change in the total body water determined by antipyrine, but there was a slight increase in the urinary excretion of sodium and chloride as contrasted to the control balance period. Identical results were subsequently obtained in this patient, employing desoxycorticosterone acetate in place of cortisone.[34] Similar studies conducted in a second patient with Cushing's syndrome yielded results identical in direction with those observed in normal individuals, although the changes were not quite so marked as seen in the latter group.[34]

The variation in effects on electrolyte metabolism in intact subjects under given experimental conditions, observed with the prolonged use of the adrenal steroids, is similarly seen in studies dealing with the acute effects of these fractions. In Fig. 5 are presented the experimental data on the urinary excretion of sodium, chloride, and potassium ob-

tained in three normal individuals following short term administration of cortisone, prednisone, compound "S" (17-hydroxy-11 desoxycorticosterone), aldosterone, and desoxycorticosterone. All patients were maintained throughout the experiment on a constant diet containing 8.5 milliequivalents of sodium with a daily oral supplement of 3 gm. of salt. The subjects were kept on this regimen for four to seven days prior to the beginning of the experimental study. The control values were obtained on the last day of the control period and all steroids with the exception of desoxycorticosterone, were administered two hours prior to the test period. Because of its oily medium, desoxycorticosterone was given four hours before the test. Both aldosterone and desoxycorticosterone were administered parenterally. On the day of the test, breakfast was withheld, and two hours after the administration of the hormone (four hours in the instance of desoxycorticosterone), each subject was given 400 ml. of water to drink; urine collections were then made over a 4-hour period and analyzed for sodium, chloride, potassium, and creatinine. Blood for serum creatinine was withdrawn during the half-mark of the test period. The total test amount of hormone was administered in one dose as follows: cortisone, 150 mg.; prednisone, 50 mg.; compound "S," 150 mg.; aldosterone, 500 micrograms intramuscularly; desoxycorticosterone, 20 mg. intramuscularly. Three days were allowed to elapse after the administration of each fraction before the next hormone was given.

Examination of the data reveals that cortisone and prednisone induced a considerable *increase* in the urinary excretion of sodium in one of the three subjects, and compound "S" in two of the three subjects. Aldosterone and desoxycorticosterone induced a significant *decrease* in the urinary excretion of this electrolyte in all three individuals. The urinary chlorides were increased appreciably in two of the three subjects following the administration of cortisone and prednisone, and in all three with compound "S." A decrease in urinary chloride was noted with aldosterone in two individuals, and in one following the use of desoxycorticosterone. A potassium diuresis was observed to occur in all three subjects when they were given cortisone and prednisone; in two with compound "S"; and in one with aldosterone and desoxycorticosterone. A second subject showed a very slight increase, of questionable significance, in the urinary excretion of potassium following the use of these last two hormones.

The results of the various studies indicate the large variety of factors which determine the nature of the response on electrolyte metabolism to the various adrenal steroids. Some of these factors, such as the presence or absence of the adrenals, the state of hydration, the salt intake, the duration of treatment, and the technical circumstances under which the experiments are performed are quite clear. However, there still remain differences in response when these factors are adequately controlled. In the final analysis, the effect is determined by the sum total of the degree of change in the glomerular filtration rate, the renal plasma flow, and the resorptive capacity of the tubules for water and electrolytes. But the various factors which influence the direction and the degree of the changes in these parameters are by no means clear. More recently, the modification of the chemical structure of the basic adrenal steroid by the organic chemist has served to modify the actions of these fractions. Halogenation of cortisone and cortisol with fluorine or chlorine in the 9 alpha position, or methylation on carbon 2, has increased the sodium retaining effect of the two original hormones enormously, while the introduction of a double bond between carbons 1 and 2 in ring "A" has the reverse effect.

In a general sense, the conclusions are justified that in adrenal insufficiency aldosterone and desoxycorticosterone are salt retaining, while cortisone and cortisol are not consistently so. In those instances in which the latter two hormones do cause a decrease in the urinary excretion of sodium, this effect is not as pronounced as that observed with aldosterone or desoxycorticosterone. Cortisone directly increases the depressed glomerular filtration rate observed in adrenal insufficiency and decreases the resorptive capacity of the renal tubules for water.

In the intact subject both cortisone and desoxycorticosterone will cause an increase in the extracellular fluid compartment, in part due to a shift of fluid and sodium from within the cell outward. The expanded extracellular space will spontaneously contract with the prolonged administration of these agents. In the presence of a spontaneous increase in adrenal cortical function such as occurs in Cushing's syndrome, this homeostatic device, both in regard to the extracellular compartment and the urinary excretion of sodium, is enhanced and may become promptly operative upon exogenous administration of the steroid.

The Meticorten and Meticortelone used in these studies were generously supplied by the Schering Corp., Bloomfield, N. J. Compound "S" by Dr. Elmer Alpert of Merck Sharp & Dohme, Rahway, N. J.; and aldosterone by Ciba, Basle, Switzerland.

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